Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Agency Secretary

Arnold Schwarzenegger
Governor

M E M O R A N D U M

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

Charles M. Andrews, Chief
Worker Health and Safety Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
1515 Clay Street, 16th Floor
Oakland, California 94612

DATE: February 4, 2004

SUBJECT: DRAFT AZINPHOS-METHYL RISK CHARACTERIZATION AND TOXIC AIR CONTAMINANT EXPOSURE DOCUMENTS, PREPARED BY DEPARTMENT OF PESTICIDE REGULATION - COMMENTS AND RECOMMENDATIONS

Thank you for the opportunity to review the draft risk characterization and toxic air contaminant documents (RCD/TAC) for azinphos-methyl (AZM) prepared by the Department of Pesticide Regulation (DPR). The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code (HSC), Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

In addition, pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides consultation to DPR on the evaluation of the health effects of candidate toxic air contaminants included in the TAC documents. As part of its statutory responsibility, OEHHA

also prepares findings on the health effects of the candidate toxic air contaminants. This documentation is to be included as part of the DPR report.

There is much history involving DPR and OEHHA in evaluating the health risks associated with exposure to the active ingredient, AZM. Although this RCD is identified as "Revision No. 1", OEHHA has reviewed three previous versions of the draft RCD for AZM, documents that were dated 1996, 1998 and 2002. OEHHA has also reviewed DPR's draft TAC document for AZM (dated July 2000) and prepared findings under FAC authority noted above. OEHHA's original findings (prepared in August of 2000) were revised last year (OEHHA, 2003a) as a result of our review of the 2002 RCD for AZM. No further revisions to the findings are warranted as a result of our review of the current RCD/TAC materials.

The only significant changes in the current version of the RCD/TAC document appear to be those introduced by combining the RCD and the TAC into a single document, the changes in the RCD added by DPR as a result of reviewer comments on the 2002 version of the RCD and the 2000 version of the TAC document, and the elimination of the MOE calculations for acute and subchronic exposures based on animal NOAELs. We note that the TAC exposure assessment remains essentially unchanged from the exposure assessment prepared for the previous, separate TAC document. We have not limited our comments to the TAC exposure assessment portion of the current document; we have briefly re-stated some of our earlier comments in order to emphasize our concern.

OEHHA comments on the current version of the AZM RCD/TAC document are as follows:

1. As discussed in detail in our comments on the prior version of this RCD (OEHHA, 2003b), we recommend that the data reported in the MacFarlane and Freestone (1998) volunteer study not be used in the RCD for quantifying human health risks from acute exposures to AZM. The reasons to not use the results of this study relate to the flaws in study design, the inappropriate utilization of statistical methods, and the lack of detail in reporting the study results. Instead, we suggest that the data from Sheets (1994) be used as the basis for calculating human health risks from acute AZM exposure. This neurotoxicity study in rats identifies a NOAEL of 1.0 mg/kg based on inhibition of brain ChE activity and effects on the functional observed battery (FOB) at the next higher dose. A NOAEL of 0.1 mg/kg was also estimated for inhibition of RBC ChE activity based on a lowest-observed-adverse-effect level (LOAEL) of 1.0 mg/kg. It is also noted that the NOAEL of 1.0 mg/kg from Sheets (1994) was used in the 1998 draft RCD as well as the 2000 draft TAC document for AZM as the critical endpoint for evaluating acute AZM exposures. This study was designed according to and meets FIFRA guidelines. The U.S. Environmental Protection Agency (U.S. EPA, 1999) also selected this neurotoxicity study for evaluating AZM acute dietary exposure.

Adoption of an acute NOAEL of 1.0 mg/kg will result in acute MOEs slightly larger than, but similar to those calculated in the RCD/TAC document using a NOAEL of 0.75 mg/kg. Of significance is the fact that MOEs calculated in the document are based on a human NOAEL, thus MOEs > 10 are considered sufficiently health-protective. The NOAEL of 1.0 mg/kg, recommended by OEHHA, is based on effects observed in experimental animals. Therefore, MOEs must be greater than 100 to be considered appropriately health-protective. OEHHA notes that MOEs calculated for several occupational exposure scenarios fall between 10 to 100 and would be interpreted differently if the MOE was based on an animal NOAEL instead of a human NOAEL. Accordingly, OEHHA recommends that DPR revisit the selection of the acute NOAEL, reconsidering the limitations of the human study used in the RCD and consider the adoption of a more health-protective NOAEL.

2. OEHHA recommends that the data reported in the MacFarlane and Freestone (1999) volunteer study not be used in the RCD for quantifying human health risks from subchronic exposures to AZM. This recommendation was also discussed in great detail in OEHHA's previous AZM RCD review (OEHHA, 2003b). As with the acute study discussed above, the reasons to not use these results relate to the flaws in study design, the inappropriate utilization of statistical methods, and the lack of detail in reporting the study results. In place of the human study, OEHHA recommends that the data from the Sheets and Hamilton study (1995) be used as the basis for calculating human health risks from subchronic (seasonal) AZM exposures. This study was designed according to and meets FIFRA guidelines. In this 13-week feeding study in rats, a NOAEL of 0.09 mg/kg was estimated from a LOAEL of 0.9 mg/kg for inhibition of RBC and plasma ChE activity. The results from this study indicate effects of AZM at doses lower than those reported in the MacFarlane and Freestone (1999) human subjects study. The results of the Sheets and Hamilton (1995) study are consistent with other laboratory animal studies.

   Adoption of a subchronic NOAEL of 0.09 mg/kg/day will result in acute MOEs significantly less than those calculated in the RCD/TAC document using a NOAEL of 0.25 mg/kg/day. As is the case with acute MOEs, subchronic MOEs calculated in the document are based on a human NOAEL, thus MOEs > 10 are considered sufficiently health-protective. The NOAEL of 0.09 mg/kg/day, recommended by OEHHA is based on effects observed in experimental animals, therefore, MOEs must be greater than 100 to be considered appropriately health-protective. OEHHA notes that subchronic MOEs calculated for several occupational exposure scenarios fall between 10 to 100 (and more would do so if a lower NOAEL was adopted) and would be interpreted differently if the MOE was based on an animal NOAEL instead of a human NOAEL.

Accordingly, OEHHA recommends that DPR revisit the selection of the subchronic NOAEL, reconsidering the limitations of the human study used in the RCD and consider the adoption of a more health-protective NOAEL.

3. Consistent with our recommendations for the selection of critical studies and NOAELs to evaluate acute and subchronic exposures, we suggest that DPR include MOEs calculated from these NOAELs in the RCD. This would be particularly important if DPR retains the critical NOAELs for acute and subchronic risk assessment since inclusion of these MOEs based on animal NOAELs will yield a more comprehensive representation of the potential risks from exposure to AZM. As indicated above, these MOEs were present in earlier versions of the RDC and TAC document, but are not included in the current combined RCD/TAC document.

4. OEHHA is concerned that seasonal and chronic exposures for the maximally-exposed individuals are not considered in the TAC exposure assessment. Individuals residing in rural areas near orchards and other crops to which azinphos-methyl is applied may experience repeated exposures to the relatively high airborne concentrations of this active ingredient following an application. Such exposures may occur several times over the course of a growing season as well as over the course of many growing seasons. Therefore, we recommend that seasonal and chronic exposures and risks be estimated for this type of receptor.

Again, thank you for the opportunity to review this document and we hope that you find our comments useful. Should you have any questions regarding OEHHA's review of this RCD, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

cc: Val F. Siebal
Chief Deputy Director
Office of Environmental Health Hazard Assessment

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment

Robert D. Schlag, M.Sc., Chief
Pesticide Epidemiology Unit
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment

David W. Rice, Ph.D.
Pesticide and Food Toxicology Unit
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment

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